Dual angiotensin receptor and neprilysin inhibition as an alternative to angiotensin-converting enzyme inhibition in patients with chronic systolic heart failure: rationale for and design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)

John J. V. McMurray1*, Milton Packer2, Akshay S. Desai3, Jim Gong4, Martin P. Lefkowitz4, Adel R. Rizkala4, Jean Rouleau5, Victor C. Shi4, Scott D. Solomon3, Karl Swedberg6, and Michael R. Zile7, on behalf of the PARADIGM-HF Committees and Investigators†

1BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; 2University of Texas Southwestern Medical Center, Dallas, TX, USA; 3Brigham and Women’s Hospital, Cardiovascular Medicine, MA, USA; 4Novartis Pharmaceutical Corporation, East Hanover, NJ, USA; 5Université de Montréal, Institut de Cardiologie, Montréal, Canada; 6University of Gothenburg, Cardiovascular Medicine Department, Gothenburg, Sweden; and 7The Medical University of South Carolina and RRJ Department of Veterans Administration Medical center, Charleston, SC, USA

Received 24 January 2013; accepted 8 February 2013; online publish-ahead-of-print 5 April 2013

Aims

Although the focus of therapeutic intervention has been on neurohormonal pathways thought to be harmful in heart failure (HF), such as the renin–angiotensin–aldosterone system (RAAS), potentially beneficial counter-regulatory systems are also active in HF. These promote vasodilatation and natriuresis, inhibit abnormal growth, suppress the RAAS and sympathetic nervous system, and augment parasympathetic activity. The best understood of these mediators are the natriuretic peptides which are metabolized by the enzyme neprilysin. LCZ696 belongs to a new class of drugs, the angiotensin receptor neprilysin inhibitors (ARNIs), which both block the RAAS and augment natriuretic peptides.

Methods

Patients with chronic HF, NYHA class II–IV symptoms, an elevated plasma BNP or NT-proBNP level, and an LVEF of ≤40% were enrolled in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF). Patients entered a single-blind enalapril run-in period (titrated to 10 mg b.i.d.), followed by an LCZ696 run-in period (100 mg titrated to 200 mg b.i.d.). A total of 8436 patients tolerating both periods were randomized 1:1 to either enalapril 10 mg b.i.d. or LCZ696 200 mg b.i.d. The primary outcome is the composite of cardiovascular death or HF hospitalization, although the trial is powered to detect a 15% relative risk reduction in cardiovascular death.
Introduction

Neurohormonal pathways are thought to be fundamentally important in the pathophysiology of heart failure. The belief that sustained activation of certain neurohumoral pathways such as the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system (SNS) is detrimental in heart failure underpins the basis of therapy. The crucial importance of the RAAS is supported by the beneficial effects of ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists. Likewise, the benefits of beta-blockers argue for a key role of the SNS. Although the focus of therapeutic intervention has been on blocking these pathways thought to be harmful in heart failure, potentially beneficial counter-regulatory systems are also activated in heart failure. These pathways variously promote vasodilatation and natriuresis, inhibit abnormal growth, suppress the RAAS and SNS, inhibit the release and actions of vasopressin, and augment the parasympathetic nervous system. The best understood mediators exerting these actions are the natriuretic peptides. The first of these to be described, A-type natriuretic peptide (ANP), is secreted in response to atrial distension, activates the ANPR-A receptor, increasing intracellular cyclic guanylate monophosphate (cGMP), and is cleared in the same way.10 Augmentation of natriuretic peptides has been considered as a therapeutic strategy in heart failure for over two decades.11,12 Because oral delivery of these peptides is ineffective and long-term parenteral delivery is problematic, blockade of natriuretic peptide breakdown, by inhibition of neprilysin, has been developed as an alternative approach to increasing natriuretic peptides. Oral neprilysin inhibitors, used in combination with ACE inhibitors, had favourable short-term effects on haemodynamic measurements and exercise time in patients with heart failure, but were not developed further.12–14 Subsequently, a molecule that was both a neprilysin and an ACE inhibitor, omapatrilat, was studied in both hypertension and heart failure, but its development was terminated because of an unacceptable incidence of angioedema. This adverse effect was thought to occur because both ACE and neprilysin break down bradykinin, which directly or indirectly can cause angioedema, and because omapatrilat may also inhibit a third enzyme metabolizing bradykinin, aminopeptidase P.19 Angiotensin receptor neprilysin inhibitors (ARNIs) are a new class of drug developed both to block the RAAS and augment natriuretic peptides.20,21 By so doing, ARNIs have the potential to modulate favourably the neurohormonal imbalance that characterizes heart failure. Because RAAS blockade is achieved by antagonism of the angiotensin II type 1 receptor, and not by inhibition of ACE (or aminopeptidase P), it is hypothesized that the risk of angioedema will not be increased.22 LCZ696 is the first ARNI to be tested in patients, and here we describe the design of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF).

Trial design and methods

PARADIGM-HF is a randomized, double-blind, parallel group, active-controlled, two-arm, event-driven trial comparing the long-term efficacy and safety of enalapril and LCZ696 in patients with chronic symptomatic heart failure and reduced EF (HF-REF). The trial was designed by the academic members of the Executive Committee in collaboration with Novartis personnel.

Patients

Entry criteria were as follows: (i) age 18 years or older and able to give written informed consent; (ii) NYHA functional class II–IV; (iii) LVEF ≤ 35% (initially this was ≤ 40% but changed in a protocol amendment dated 15 December 2010); (iv) plasma BNP ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) at the screening visit (Visit 1, Figure 1) or a BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) and a hospitalization for heart failure within the last 12 months; (v) treatment with a stable dose of an ACE inhibitor or an ARB equivalent to enalapril 10 mg/day (see Table 1) for at least 4 weeks before the screening visit; and (vi) treatment with a stable dose of a beta-blocker for at least 4 weeks prior to the screening visit, unless contraindicated or not tolerated. Although not required, the protocol specified that an aldosterone antagonist should also be considered in all patients, taking account of renal function, serum potassium, and tolerability. If given, the dose of aldosterone antagonist should be stable for at least 4 weeks prior to the screening visit. The key exclusion criteria are listed in Table 2.

Study design

The study consists of four phases: (i) screening; (ii) single-blind enalapril run-in; (iii) single-blind LCZ696 run-in; and (iv) randomized double-blind treatment (Figure 1). The rationale for the active run-in periods is explained in the Discussion.
Screening (Visit 1)

At the screening visit, patient eligibility was assessed according to the inclusion/exclusion criteria (including the criteria in Table 3). Any local measurement of LVEF within the eligibility range made within the past 6 months was acceptable provided there was no subsequent LVEF measurement above it. Eligibility BNP (and NT-proBNP), serum potassium, and estimated glomerular filtration rate (eGFR) were measured in a central laboratory.

Enalapril active run-in period (Visit 2)

At Visit 2, most eligible patients started 2 weeks of single-blind treatment with enalapril 10 mg b.i.d. A lower dose of enalapril (5 mg b.i.d.) was allowed for patients currently treated with an ARB and for those taking a low dose of ACE inhibitor (see Table 1) if the investigator was concerned that switching directly to enalapril 10 mg b.i.d. might not be tolerated (e.g. because of hypotension, renal dysfunction, and/or hyperkalaemia). These patients were up-titrated to enalapril 10 mg b.i.d. after 1–2 weeks. Patients tolerating enalapril 10 mg b.i.d. as defined by the criteria in Table 3 were eligible for Visit 3.

LCZ696 active run-in period (Visits 3 and 4)

At Visit 3, patients started single-blind treatment with LCZ696 100 mg b.i.d. After 1–2 weeks, the dose was up-titrated to 200 mg b.i.d., for a further 2–4 weeks.

Other heart failure medication (except for an ACE inhibitor or ARB) was continued during the run-in periods.

Randomization to double-blind treatment (Visit 5)

Patients tolerating both enalapril 10 mg b.i.d. and LCZ696 200 mg b.i.d., as defined by the criteria in Table 3, were randomized in a 1:1 ratio to double-blind treatment with either enalapril 10 mg b.i.d. or LCZ696 200 mg b.i.d. Study visits occur every 2–8 weeks during the first 4 months of the double-blind period and every 4 months thereafter (with additional unscheduled visits, at the discretion of the investigator).

There were two short washout periods during the run-in periods to minimize the potential risk of angioedema due to overlapping ACE inhibition and NEP inhibition at Visit 3 and Visit 5: (i) enalapril was stopped a day prior to starting LCZ696 at Visit 3 and (ii) LCZ696 was stopped a day prior to starting randomized study drug at Visit 5.

Monitoring of safety and tolerability during double-blind period

Patients are assessed at each study visit for hyperkalaemia, symptomatic hypotension, increase in serum creatinine, angioedema, and other adverse events (AEs) and serious AEs. Patients who can no longer tolerate the target dose of study drug can be down-titrated to the lower dose at the investigator’s discretion (after considering whether any other relevant non-disease-modifying

---

**Table 1 Minimum required pre-study daily doses of commonly prescribed angiotensin-converting enzyme inhibitors and angiotensin receptor blockers**

<table>
<thead>
<tr>
<th>ACE inhibitors</th>
<th>Minimum daily dose</th>
<th>ARBs Minimum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>10 mg</td>
<td>Candesartan 16 mg</td>
</tr>
<tr>
<td>Captopril</td>
<td>100 mg</td>
<td>Eprosartan 400 mg</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>2.5 mg</td>
<td>Irbesartan 150 mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>20 mg</td>
<td>Losartan 50 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10 mg</td>
<td>Olmesartan 10 mg</td>
</tr>
<tr>
<td>Moexipril</td>
<td>7.5 mg</td>
<td>Telmisartan 40 mg</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4 mg</td>
<td>Valsartan 160 mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td>Ramipril</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td>Trandolapril</td>
<td>2 mg</td>
<td></td>
</tr>
<tr>
<td>Zofenopril</td>
<td>30 mg</td>
<td></td>
</tr>
</tbody>
</table>

---

**Figure 1 PARADIGM-HF study schema.**
hospitalization.

conventional heart failure treatment, in delaying time to first oc-

200 mg b.i.d. compared with enalapril 10 mg b.i.d., in addition to

The purpose of this study is to evaluate the effect of LCZ696

Primary objectives
The purpose of this study is to evaluate the effect of LCZ696

Secondary objectives
Secondary endpoints were to test whether LCZ696, compared with

Study management and committees
PARADIGM-HF is conducted by Novartis AG under the guidance and

Exploratory objectives
These are listed in Table 4.

Study objectives
Primary objectives
The purpose of this study is to evaluate the effect of LCZ696

Table 2  Key exclusion criteria

| 1. History of hypersensitivity or allergy to any of the study drugs, drugs of similar chemical classes, ACE inhibitors (ACEIs), ARBs, or neprilysin inhibitors, as well as known or suspected contraindications to the study drugs. |
| 2. Previous history of intolerance to recommended target doses of ACEIs or ARBs. |
| 3. Known history of angioedema. |
| 4. Requirement for treatment with both ACEIs and ARBs. |
| 5. Current acute decompensated heart failure (exacerbation of chronic heart failure manifested by signs and symptoms that may require intravenous therapy). |
| 6. Symptomatic hypotension and/or a systolic blood pressure < 100 mmHg at Visit 1 (screening) or < 95 mmHg at Visit 3 or at Visit 5 (randomization). |
| 7. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² at Visit 1 (screening), Visit 3 (end of enalapril run-in), or Visit 5 (end of LCZ696 run-in and randomization) or > 35% decline in eGFR between Visit 1 and Visit 3 or between Visit 1 and Visit 5. |
| 8. Serum potassium > 5.2 mmol/L at Visit 1 (screening) or > 5.4 mmol/L at Visit 3 or Visit 5 (randomization). |
| 9. Acute coronary syndrome, stroke, transient ischaemic attack, cardiac, carotid, or other major cardiovascular surgery, PCI, or carotid angioplasty within the 3 months prior to Visit 1. |
| 10. Coronary or carotid artery disease likely to require surgical or percutaneous intervention within the 6 months after Visit 1. |
| 11. Implantation of a CRT device within 3 months prior Visit 1 or intent to implant a CRT. |
| 12. History of heart transplant or on a transplant list or with LV assistance device. |
| 14. Diagnosis of peripartum- or chemotherapy-induced cardiomyopathy within the 12 months prior to Visit 1. |
| 15. Documented untreated ventricular arrhythmia with syncopal episodes within the 3 months prior to Visit 1. |
| 16. Symptomatic bradycardia or second- or third-degree atrioventricular block without a pacemaker. |
| 17. Presence of haemodynamically significant mitral and/or aortic valve disease, except mitral regurgitation secondary to LV dilatation. |
| 18. Presence of other haemodynamically significant obstructive lesions of the LV outflow tract, including aortic and subaortic stenosis. |
| 19. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including, but not limited to, any of the following: |
| History of active inflammatory bowel disease during the 12 months before Visit 1. |
| Active duodenal or gastric ulcers during the 3 months prior to Visit 1. |
| Evidence of hepatic disease as determined by any one of the following: aspartate aminotransferase or alanine aminotransferase values exceeding 2 × upper limit of normal at Visit 1, history of hepatic encephalopathy, history of oesophageal varices, or history of porto-caval shunt. |
| Current treatment with cholestyramine or colestipol resins. |
| 20. Presence of any other disease with a life expectancy of < 5 years. |

Collection and adjudication of potential angioedema events
Potential angioedema cases are identified in two ways: (i) proactive reporting of any events that resemble angioedema by site investiga-
tors; and (ii) routine safety monitoring by the sponsor for signs or symptoms suggestive of potential angioedema. All identi-
fied cases are submitted to an independent angioedema adjudica-
tion committee for a final decision.

therapy can be discontinued, e.g. a calcium channel or alpha-adre-

neceptor blocker in a hypotensive patient). The dose of back-
ground disease-modifying drugs, such as beta-blockers, should not be reduced to facilitate maintenance of study drug. Every attempt should be made to re-challenge the patients so as to main-
tain as many patients as possible on the target dose of study drug.

The dose of background disease-modifying drugs, such as beta-blockers, should not be reduced to facilitate maintenance of study drug. Every attempt should be made to re-challenge the patients so as to main-
tain as many patients as possible on the target dose of study drug.

Evidence of hepatic disease as determined by any one of the following: aspartate aminotransferase or alanine aminotransferase values exceeding 2 ×

upper limit of normal at Visit 1, history of hepatic encephalopathy, history of oesophageal varices, or history of porto-caval shunt.

Current treatment with cholestyramine or colestipol resins.

Secondary objectives
Secondary endpoints were to test whether LCZ696, compared with

enalapril, is superior: (i) in improving the Kansas City Cardiomyop-
athy Questionnaire (KCCQ) clinical summary score for heart failure symptoms and physical limitations at 8 months;23 (ii) in delay-

ing the time to all-cause mortality; (iii) in delaying time to new onset atrial fibrillation; and (iv) in delaying the time to first occurrence of either: (a) a 50% decline in eGFR relative to baseline (i.e. Visit 5); (b) > 30 mL/min/1.73 m² decline in eGFR relative to baseline to a value < 60 mL/min/1.73 m²; or (c) reaching end-stage renal disease.

Exploratory objectives
These are listed in Table 4.

Study management and committees
PARADIGM-HF is conducted by Novartis AG under the guidance and leadership of the Executive Committee. The National Leaders of participating countries are listed in Appendix 1. An independent, external Data Monitoring Committee (DMC) (listed in Appendix 1) has been appointed to oversee the safety of the patients and review the results of the interim analyses. An Endpoint Adjudication Committee (listed in Appendix 1) is responsible for classifying all deaths and for determining whether pre-
specified endpoint criteria are met for the non-fatal events. Another committee is adjudicating suspected cases of angioedema in this and other trials using LCZ696 (listed in Appendix 1).

**Statistical considerations**

The estimated annual event rate for the primary endpoint in the control (enalapril) arm of PARADIGM-HF was based on the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM)-Added trial where the annual event rate for the primary endpoint in the enalapril arm of PARADIGM-HF was based on the Can-

The sample size is based upon the CV mortality (although the same composite was 16.6% in the placebo group (and 14.1% in the candesartan group). Because patients are treated with a higher dose of ACE inhibitor (or LCZ696 equivalent) in PARADIGM-HF and a greater proportion were expected to receive a beta-blocker and a mineralocorticoid antagonist, a more conservative expected annual event rate of 14.5% was chosen for sample size calculation. The annual CV mortality rate of 7% was estimated from the CHARM-Added trial in a similar manner. We also anticipated that the requirement for an elevated BNP or NT-proBNP level at enrolment would ensure an adequate event rate.

The sample size is based upon the CV mortality (although the trial will continue until the required number of patients have...
Discussion

A strategy of dual RAAS blockade and natriuretic peptide augmentation is theoretically attractive in heart failure and was tried previously with the dual nephrilysin/ACE inhibitor omapatrilat in the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events trial (OVERTURE).\(^{17}\) Although omapatrilat did not reduce the primary endpoint of death or hospitalization for heart failure requiring intravenous treatment, compared with enalapril 10 mg b.i.d., it was superior to enalapril in relation to the secondary endpoint of CV death or CV hospitalization. Furthermore, when the effect of omapatrilat on the primary endpoint was evaluated, retrospectively, using the same definition of hospitalization for heart failure as had been used in the Studies of Left Ventricular Dysfunction Treatment-trial (SOLVD-Treatment), where the use of intravenous therapy was not required for positive adjudication, omapatrilat was superior to enalapril. Furthermore, administration of a single, large, dose of omapatrilat once daily may have on the one hand caused excessive post-dose hypotension and on the other not provided complete 24 h RAAS blockade or 24 h nephrilysin inhibition. Ultimately, however, because omapatrilat caused an unacceptable incidence of angioedema in patients with hypertension, its development was halted.\(^{18}\)

LCZ696 is a first-in-class ARNiL.\(^{20–22}\) After ingestion, LCZ696 delivers systemic exposure to AHU377, a nephrilysin inhibitor pro-drug, and valsartan, an ARB. AHU377 is then rapidly metabolized by non-specific esterases to the active nephrilysin inhibitor LBQ657. LCZ696 causes dose-dependent increases in ANP, plasma and urinary cGMP, plasma renin activity, and angiotensin II, effects consistent with activation of the NPR-A receptor and blockade of the angiotensin II type 1 receptor.\(^{20–22}\) In healthy volunteers and patients with heart failure, a total daily dose of 400 mg of LCZ696 gives systemic exposure to valsartan similar to Diovan\(^{\text{®}}\) 320 mg daily.

Several features of the design of PARADIGM-HF are worthy of discussion.

The patients included in PARADIGM-HF are similar to those enrolled in SOLVD-Treatment, i.e. in NYHA class II–IV and with an LVEF ≤ 35% (in most cases). However, PARADIGM-HF also had natriuretic peptide entry criteria. We used a BNP entry threshold of ≥ 150 pg/mL (or NT-proBNP ≥ 600 pg/mL) at Visit 1 or a BNP ≥ 100 pg/mL (or NT-proBNP ≥ 400 pg/mL) if the patient was hospitalized for heart failure within the last 12 months. This is because BNP and NT-proBNP are powerful predictors of CV events in patients with heart failure and are, therefore, useful in helping select a higher risk population.\(^{27,28}\) This was necessary, in the light of recent improvements in outcome in patients with heart failure as a result of new drug and device therapies, to ensure a realistic trial size, and a trial with adequate power to show a modest but still important treatment effect. Note that patients in PARADIGM-HF are required to be treated with a betablocker unless contraindicated or not tolerated, and investigators are encouraged to use a mineralocorticoid (aldosterone) receptor antagonist, as indicated.

The choice of active comparator was based upon the SOLVD-Treatment trial which was a pivotal ACE inhibitor mortality/morbidity study in a broad spectrum of patients with HF-REF.\(^{29}\) In
that trial, the target dose of enalapril was 10 mg b.i.d. and the mean daily prescribed dose in patients taking enalapril was 16.6 mg. The same target dose of enalapril was used in at least seven other large heart failure trials (Table 5). These trials and another large community study of >17,500 patients achieved a mean daily dose of enalapril of between 15 and 18 mg. Two trials, which had higher target doses (20 mg b.i.d. and 30 mg b.i.d.), achieved only slightly greater average doses, with less than half of patients titrated to target. Therefore, from a regulatory perspective, the ‘gold standard’ comparator for LCZ696 is enalapril 10 mg b.i.d., the most tested ACE inhibitor in HF-REF. Moreover, we anticipate that achievement of a similar average dose to that attained in the SOLVD-Treatment trial will be required, although in two more recent trials where enalapril was used in addition to a beta-blocker (which was rarely used in SOLVD-Treatment), a lower average achieved dose of enalapril was attained.

The choice of dose of LCZ696 was first and foremost based on the need to achieve serum concentrations of valsartan equivalent to those obtained with the Diovan formulation of valsartan 160 mg b.i.d., the dose shown to be effective in Val-HeFT and VALIANT. Secondly, the dose of LCZ696 also had to achieve adequate inhibition of neprilysin. LCZ696 200 mg b.i.d. achieves systemic exposure similar to valsartan 160 mg b.i.d. and, at that dose, also achieves 90% of its maximum inhibition of neprilysin and leads to sustained increases in plasma cGMP concentrations in healthy volunteers. In addition, in patients with hypertension, LCZ696 200 mg once daily lowered sitting systolic (difference 5.3 mmHg) and diastolic (difference 3.0 mmHg) blood pressure more than valsartan 160 mg, an incremental blood pressure-lowering effect attributed to neprilysin inhibition. Furthermore, in a proof-of-concept study in patients with HF-PEF, the Prospective comparison of ARNi with ARB on Management Of heart failUre with preserved ejectioN fraction trial (PARAMOUNT), LCZ696 200 mg b.i.d., compared with valsartan 160 mg b.i.d., led to a sustained reduction over 36 weeks in plasma NT-proBNP concentration (a marker of LV diastolic wall stress and not a substrate for neprilysin) and left atrial (LA) size (as a potential marker of LA and LV end-diastolic pressure).

The active run-in period of PARADIGM-HF served two main functions. First, both the enalapril and LCZ696 run-in periods maximized attainment of the target doses of each drug which is important as outlined above. The LCZ696 run-in period also provided investigator-unblinded, albeit short-term, safety information on the ARNI, which was important in light of the limited data on tolerability of LCZ696 in patients with heart failure available before PARADIGM-HF commenced—in essence the development programme for LCZ696 in systolic heart failure bypassed the typical ‘Phase II’ development stage. The decision to do this, rather than conduct an initial ‘stand-alone’ Phase II trial, was based on substantial and reassuring safety experience with LCZ696 in hypertension and prior experience with omapatrilat. Furthermore, Phase II studies rarely predict success in Phase III trials in heart failure and simply prolong the time and increase the cost involved in making a definitive determination of the efficacy and safety of a new treatment, which always requires a large mortality/morbidity trial.

For safety reasons, there are also two short washout periods during the run-in. These washout periods are designed to minimize concomitant neprilysin and ACE inhibition which is likely to increase the risk of angioedema. Although the risk of angioedema is expected to be low, for the reasons outlined earlier, a special committee of experts are adjudicating all cases of suspected angioedema in PARADIGM-HF and other studies with LCZ696 (see Appendix 1).

The primary outcome of CV death or heart failure hospitalization was chosen as the one that best reflects the major mortality and morbidity burden of this syndrome and has been used in other recent trials including CHARM-Added, SHIFT, and EMPHASIS-HF. However, uniquely, PARADIGM-HF is powered on the basis of CV mortality giving both adequate power to detect a reduction in CV mortality and >97% power to detect a clinically meaningful reduction in the primary composite outcome. Two of the secondary and exploratory endpoints merit a special mention. Decline in renal function is of interest given that natriuretic peptides and neprilysin inhibition have been reported to increase glomerular filtration and because renal impairment as an adverse effect was less common with omapatrilat than with enalapril in OVERTURE. Similarly, development of diabetes is of interest, given the recent suggestion that low natriuretic peptides levels may be associated with the development of this disease and omapatrilat improved glucose utilization peripherally.

In summary, PARADIGM-HF is addressing, within a major clinical outcome trial, the place of the ARNI LCZ696 as an alternative to the ‘gold-standard’ ACE inhibitor enalapril in patients with chronic systolic heart failure. As the largest clinical trial in heart failure to date, PARADIGM-HF may change our approach to neurohumoral modulation in heart failure.

Funding
PARADIGM-HF is funded by Novartis Pharma AG.

Conflict of interest: all Executive Committee members or their institutions have received consulting fees as well as travel and research support in the planning and conduct of PARADIGM-HF. J.G., M.P.L., A.R.R., and V.C.S. are employees of Novartis.

Appendix 1. Complete list of the PARADIGM-HF Committees and Investigators

Executive Committee: John McMurray (Co-Chair), Milton Packer (Co-Chair), Jean Rouleau, Scott Solomon, Karl Swedberg, Michael Zile.
Data Monitoring Committee: Henry Dargie (Chair), Robert Foley, Gary S. Francis, Michele Komajda, Stuart Poocock.
Angioedema Adjudication Committee: Allen P. Kaplan (Chair), Nancy Brown, Bruce Zuraw.
Endpoint Adjudication Committee: Scott Solomon (Chair), Akshay S. Desai (Co-Chair), Peter Finn, Larry Weinrauch, Howard Hartley, Ebrahim Barkoudah, Chau Duong.
Investigators: NL = National Leader.
Angiotensin receptor neprilysin inhibition in heart failure

Argentina

Belgium

Brazil

Bulgaria

Canada

Chile

China
Jun Huang (NL), M. Gui, H. Hu, Y. Ke, L. Li, X.D. Li, X.L. Li, W. Li, X. Liu, S. Liu, G. Ma, N. Sun, G. Xu, K. Yang, Z. Yuan, J. Zhang, R. Zhao.

Colombia

Czech Republic

Denmark

Dominican Republic
Angel Gonzalez (NL), P. Martinez, A. Paulino.

Ecuador
Yan Carlo Duarte (NL), C. Delgado, Y. Duarte, L. Hidalgo, C. Mariscal, R. Marmol.

Estonia
Arvo Rosenthal (NL), A. Kaasik, J. Kaik, E. Laane.

Finland
Keijo Peukurinen (NL), T. Jääskeläinen, K. Kiilavuori, J. Taurio.

France

Germany
Michael Böhm (NL), V. Adelberger, A. Al-Zoebi, A. Bastian, S. Behrens, H. Bessler, R. Braun, M. Buhr, G. Cieslinski, W. Daut, H. Demmig, S. Denny, H. Ebert, C. Fechtrup, S. Fischer,

Guatemala

Hong Kong
S. Li, H. Tse, B. Yan, G. Yip.

Hungary

Iceland
Karl Andersen (NL), T. Gudnason, A. Sigurdsson, G. Thorgerirsson.

India

Israel

Italy

Latvia
Andrejs Erglis (NL), G. Dormidontova, R. Egile, T. Lvova, G. Rancane, I. Sime.

Lithuania
Zaneta Petruilioniene (NL), D. Luksiene, R. Mazutavicius, R. Miluniene, R. Slapikas.

Malaysia
D. Chew, O. Ismail, T. Ong, A. Wan.

Mexico

The Netherlands

Panama
E. Aviles, G. Frago, B. Gonzalez, R. Nieto.

Peru

Philippines
Poland

Portugal
Jose´ Silva-Cardoso (NL), F. Almeida, A. Andrade, N. Braganca, S. Carvalho, J. Ferreira Santos, C. Fonseca, L. Oliveira, F. Padua, R. Soares.

Romania

Russia

Singapore
Raymond Wong (NL), C. Lee, H. Ong, D. Yeo.

South Africa

South Korea

Spain

Sweden

Taiwan
C-H Chen (NL), C.P. Chen, P. Chen, K. Hsu, L. Lin, P. Pai, H. Tsao, B. Tzeng.

Thailand

Turkey

UK
References


Venezuela

Ivan Mendoza (NL), M. Alvarez, A. Avendaño, E. Silva, G. Vergara.

References


